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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,801	09/10/2003	Paolo Gatti	PC23575A	1817

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PFIZER INC
10555 SCIENCE CENTER DRIVE
SAN DIEGO, CA 92121

EXAMINER	
SCHLIENTZ, NATHAN W	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
12/20/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

~ipgslaj@pfizer.com

Office Action Summary	Application No.	Applicant(s)	
	10/658,801	GATTI, PAOLO	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *121 and 124-126* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *121 and 124-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/19/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 121 and 124-126 are pending in this application and are examined herein on the merits for patentability. No claim is allowed at this time.

Withdrawn Rejections

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 19 October 2010 was filed after the mailing date of the non-final Office action on 24 May 2010. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 121 and 124-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Tang et al. (WO 01/60814) and Shenoy et al. (WO 01/37820 A2).

Determination of the scope and content of the prior art

(MPEP 2141.01)

Tang et al. teach compositions comprising pyrrole substituted 2-indolinone compounds and their pharmaceutically acceptable salts (Abstract). Tang et al. teach that the pharmaceutically acceptable salt is prepared by reacting the free base of the parent compound with inorganic acids, preferably hydrochloric acid or (L)-malic acid, such as the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (pg. 25, ln. 6-8). Tang et al. further teach on page 77 compositions comprising:

TABLE 2

Ingredient Name/Grade	Concentration in Granulation (% w/w)	Amount in 50 mg Capsule (mg)	Amount in 200 mg Capsule (mg)
Formulation Code	J-011248-AA	J-011248-AA-00	J-011248-AA-01
Active Compound NF	65.0	50.0	200.0
Mannitol NF	23.5	18.1	72.4
Croscarmellose sodium NF	6.0	4.6	18.4
Povidone K 30 NF	5.0	3.8	15.2
Magnesium stearate NF	0.5	0.38	1.52
Capsule, Swedish yellow NF		Size 3	Size 0

Tang et al. teach that pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, e.g., the modulation of PK activity or the treatment or prevention of a PK-related disorder. Determination of a therapeutically effective amount is well within the capability of those skilled in the art (pg. 80, ln. 29 to pg. 82, ln. 3). Tang et al. also teach cellular assay results, *in vivo* efficacy studies, efficacy in a model of disseminated disease, and biological activity of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (compound 80) (pg. 194 to pg. 208). Tang et al. teach that compound 80 crosses cellular membranes and penetrates into cells; has statistically significant inhibition of tumor growth; inhibited the growth of all the tumor types shown in Table 7; exhibited a pronounced inhibition of tumor cell proliferation; has profound anti-angiogenic and anti-tumor effects, even under conditions in which tumors do not

regress; and a single oral dose resulted in high oral bioavailability. Tang et al. state that oral administration of compound 80 causes a direct effect on target activity in tumors *in vivo*, and dosing regimens may be determined by those with ordinary skill in the art without undue experimentation.

Shenoy et al. teach a formulation comprising 15-75 wt.% ionizable substituted indolinone, 5-95 wt.% binder, 4-10 wt.% disintegrant, and 1-1.5 wt.% lubricant (page 96, 2nd Table, "Indolinone + Surfactant + Diluent + Binder + Disintegrant + Lubricant + Flow Enhancer"). Shenoy et al. further teach that 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide is a suitable ionizable substituted indolinone (page 39, compound 80; and pages 158-159, Example 80). Shenoy et al. also teach that the ionizable substituted indolinone contemplated for use are pharmaceutically acceptable salts which do not abrogate the biological activity and properties of the compound (page 60, lines 1-6), wherein the ionizable substituted indolinone is reacted with a molar equivalent of a base solution or an acid solution, such as malic acid (page 65, lines 1-4; page 76, lines 1-3).

Shenoy et al. also teach suitable pharmaceutically acceptable diluents include mannitol (page 73, lines 14-15); suitable pharmaceutically acceptable binders include polyvinylpyrrolidone (i.e. povidone) (page 73, lines 17-18); suitable pharmaceutically acceptable disintegrants include croscarmellose (page 73, lines 19-21); and suitable pharmaceutically acceptable lubricants include magnesium stearate (page 73, lines 26-27).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Tang et al. do not specifically teach the exact formulation comprising 40% w/w indolinone compounds, 47.5% w/w mannitol, 6% w/w croscarmellose sodium, 5% w/w povidone, and 1.5% w/w magnesium stearate, as instantly claimed. However, Shenoy et al. teach indolinone-containing compositions comprising 15-75% w/w indolinone, 5-95 wt.% binder, 4-10 wt.% disintegrant, and 1-1.5 wt.% lubricant (page 96, 2nd Table, "Indolinone + Surfactant + Diluent + Binder + Disintegrant + Lubricant + Flow Enhancer"). Therefore, one of ordinary skill in the art could discover the workable ranges of Shenoy et al. through routine experimentation.

The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Tang et al. clearly teach solid formulations comprising the exact same components as instantly claimed. One of

ordinary skill in the art would routinely be able to adjust the amounts of the components of the solid formulation within the limits of Shenoy et al. and still have a therapeutically effective solid formulation.

Tang et al. do not specifically teach capsules containing 25, 50 or 100 mg 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate, as instantly claimed. However, Tang et al. teach capsules containing 50 mg or 200 mg active compound (Table 2). Also, Tang et al. teach that dosing regimens may be determined by those with ordinary skill in the art without undue experimentation. Tang et al. further teach that determination of a therapeutically effective amount is well within the capability of those skilled in the art (pg. 80, ln. 29 to pg. 82, ln. 3). Therefore, one of ordinary skill in the art would be able to determine the appropriate amount of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate per capsule in order to achieve a therapeutically effective dosage form.

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to determine the therapeutically effective amount of indolinone compound, such as sunitinib L-malate, for incorporation in the compositions according to Tang et al.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant argues that the instant invention surprisingly results in a pharmaceutically acceptable, stable formulation that does not suffer from flow or adhesion problems during the capsule filling process. Applicant then discusses three references which they argue teach that optimizing the amount of a lubricant does not lead to an expectation of success in solving the flow or adhesion problems during processing.

However, the examiner respectfully asserts that one of ordinary skill in the art would optimize the amounts of lubricant and other excipients to overcome any processing problems, such as flow and adhesion problems. As noted by applicant, Podczeck teaches that flow problems can be removed by optimal lubricants and adhesion might be solved by optimizing lubricants and glidants, and that adhesion problems can be overcome by modification of the formulation; Aulton teaches that lubricants and glidants improve filling properties and effect release, and magnesium stearate has marked effect on release, dissolution and/or cohesiveness; and Swarbrick teaches that lubricants prevent adhesion and improve flow, and magnesium stearate is the most commonly used excipient. Therefore, Podczeck, Aulton, and Swarbrick teach to one of ordinary skill in the art that optimizing the amounts of excipients, especially lubricants, can fix flow and adhesion problems.

Applicant further argues that a comparative study in the instant specification shows that the claimed invention unexpectedly solves the granulate adhesion problem encountered with the initial development formulation used for clinical studies which comprised 75% sunitinib malate. However, the comparative study did not compare with the closest prior art (Tang et al.). Also, the formulations compared, Example 1 vs. Example 2, do not comprise the same amount of lubricant, which is known to affect the flow and adhesion during processing. One of ordinary skill in the art would expect there to be a change in flow and adhesion when the amount increases from 0.5% to 1.5%. It is the position of the examiner that applicant merely optimized the amount of each ingredient within art recognized ranges to overcome the sticking problem, which was well within the purview of one of ordinary skill in the art. It is noted that Tang et al. comprise the exact same components as instantly claimed, but in different amounts. It was well known in the art at the time of filing that adjusting the amounts of each component will have an effect on flow and adhesion. Therefore, one or ordinary skill in the art would routinely optimize the amounts of each component within the formulation to overcome any processing problems.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the

disclosed subject matter from the applicant. See MPEP 716.01(c)(II). "The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001." *Ex parte Gray*, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 9:00 AM to 5:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616